Regional Pulmonary Perfusion, Inflation, and Ventilation Defects in Bronchoconstricted Patients with Asthma

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Rationale: Bronchoconstriction in asthma leads to heterogeneous ventilation and the formation of large and contiguous ventilation defects in the lungs. However, the regional adaptations of pulmonary perfusion ($\dot{Q}$) to such ventilation defects have not been well studied.

Methods: We used positron emission tomography to assess the intrapulmonary kinetics of intravenously infused tracer nitrogen-13 (^{13}NN), and measured the regional distributions of ventilation and perfusion in 11 patients with mild asthma. For each subject, the regional washout kinetics of ^{13}NN before and during methacholine-induced bronchoconstriction were analyzed. Two regions of interest (ROIs) were defined: one over a spatially contiguous area of high tracer retention (TR) during bronchoconstriction and a second one covering an area of similar size, showing minimal tracer retention (NR).

Results: Both ROIs demonstrated heterogeneous washout kinetics, which could be described by a two-compartment model with fast and slow washout rates. We found a systematic reduction in regional $\dot{Q}$ to the TR ROI during bronchoconstriction and a variable and nonsignificant change in relative $\dot{Q}$ for NR regions. The reduction in regional $\dot{Q}$ was associated with an increase in regional gas content of the TR ROI, but its magnitude was greater than that anticipated solely by the change in regional lung inflation.

Conclusion: During methacholine-induced bronchoconstriction, perfusion to ventilation defects are systematically reduced by a relative increase in regional pulmonary vascular resistance.

Keywords: emission computed tomography; pulmonary gas exchange; vascular resistance; vasoconstriction; ventilation-perfusion ratio

It is well established that severe heterogeneity of regional ventilation contributes significantly to gas exchange impairment in asthma. However, the extent to which regional pulmonary perfusion adapts to match changes in ventilation during an asthma attack is unknown. Evidence for severe heterogeneity of regional ventilation in patients with asthma has come from measurements with external scintillation counters (1, 2), single-photon emission computed tomography (CT) of Technegas (3), nuclear magnetic resonance imaging after a single-breath inhalation of hyperpolarized helium (4), and high-resolution CT (5–10). Most of these studies, however, did not quantify regional ventilation during

normal breathing and did not evaluate the effect of bronchoconstriction on regional pulmonary perfusion.

Changes in regional perfusion during bronchoconstriction (BC) have been measured using technetium ($^{99\text{m}}\text{Tc}$)-labeled macroaggregated albumin (11, 12). In one study, perfusion defects of segmental or smaller size were reported mainly at the periphery of middle or lower lung zones in children with asthma, despite normal chest X-rays, blood gases, and peak expiratory flows (13). That study, however, did not assess whether these perfusion defects corresponded to defects in ventilation. Another study assessed ventilation with krypton ($^{81\text{m}}\text{Kr}$) gas and perfusion with $^{99\text{m}}\text{Tc}$ macroaggregated albumin in subjects with asthma after treatment with bronchodilator and pointed out that perfusion defects appeared to be secondary to changes in regional ventilation (14). However, that study was only qualitative and perfusion was imaged with low-resolution scintigraphy only after treatment with isoprenaline aerosol. Another group, using the same technique, qualitatively described regional ventilation and perfusion in subjects with asthma after histamine inhalation (15), antigen challenge (16), and exercise (17). The studies reported perfusion changes that partially matched those of ventilation, but only after antigen challenge, despite ventilation changes that were seen with all three bronchoconstricting triggers. Therefore, controversy persists over whether and to what extent regional pulmonary perfusion is altered in asthma and on its spatial correlation with regional ventilation.

The frequency distribution of the ventilation-to-perfusion ratio ($\dot{V}_A/\dot{Q}$) has been assessed in subjects with asthma with the multiple inert gas elimination technique. Widening or bimodality of $\dot{V}_A/\dot{Q}$ distributions in asymptomatic asthma (18), chronic asthma (19), acute severe asthma (20), and during methacholine-induced bronchoconstriction (21) have been reported. Although quantitative, these studies could not identify the topographical distribution or size of low $\dot{V}_A/\dot{Q}$ units or determine the extent to which the distribution of $\dot{Q}$ was changing with bronchoconstriction.

Using positron emission tomography (PET) imaging of intrapulmonary ^{13}NN -saline kinetics, we recently showed that, during acute bronchoconstriction, regions with severe hypoventilation (“ventilation defects”) are formed from clusters of severely hypoventilating units (22). On the basis of basic physiology, we theorized that the regional increase in airway resistance to ventilation defects could have been accompanied by relative hyperinflation of those regions. We expected that to match the reduction in ventilation, perfusion to ventilation defects could be reduced. Therefore, the principal aim of this study was to assess whether redistribution of regional pulmonary perfusion away from ventilation defects occurred during methacholine-induced bronchoconstriction in subjects with asthma and whether these changes were accompanied by changes in regional lung inflation. Some of the results of this study have been previously reported in abstract form (23).

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METHODS

Subject Characteristics

Eleven patients with mild asthma (five male and six female) were studied with protocols and procedures approved by the Human Research Committee of the Massachusetts General Hospital. Details of inclusion and exclusion criteria can be found in the online supplement. Informed consent was obtained from each subject before the study. The average age was 27 ± 12 (mean $\pm$ SD) yr. Characteristics of the individual subjects can be found in Table E1 of the online supplement. Most subjects had normal spirometry on the day of the study (Table E2), despite having their asthma medications withheld according to American Thoracic Society methacholine challenge test guidelines (24).

Protocol

We used a PET scanner (Scanditronix PC4096; General Electric, Milwaukee, WI) that imaged 15 contiguous 6.5-mm-thick slices of the thorax. Emission scans were acquired to measure regional pulmonary perfusion and ventilation from the kinetics of ^{13}N injected as a bolus in saline solution during a brief (~ 30 s) apnea, as described in detail elsewhere (25–27) and summarized in the online supplement. Briefly, because of its low solubility in tissues (partition coefficient $\lambda_{\text{water/air}} = 0.015$ at 37°C), on arrival into the pulmonary capillaries virtually all ^{13}N diffuses into the alveolar airspace at first pass and regional tracer concentration during apnea is proportional to regional perfusion. When breathing resumes, regional ventilation can be derived from the tracer washout rate, because ^{13}N is eliminated from the lung almost exclusively by ventilation. A schema of the study protocol is shown in Figure 1 and representative tracer kinetics are shown in Figure E1.

Data Analysis

Voxel-by-voxel image analysis. Images proportional to regional pulmonary perfusion were generated from the mean tracer activity per voxel acquired during the apneic plateau phase after tracer infusion (27). The heterogeneity of the perfusion distribution was characterized by the mean-normalized variance of the tracer concentration ($\text{CV}_0^2 = [\text{SD}/\text{mean}]^2$) corrected for statistical noise (27) and a vertical perfusion gradient was calculated, with negative values indicating a decrease in perfusion going from dependent to nondependent. The fraction of tracer remaining within the imaged lung field after 3 min of washout (Ftr) was calculated by normalizing the residual tracer activity by the

activity measured during the plateau of the apnea phase. Ftr was plotted versus its respective FEV_1 normalized by the FVC measured before methacholine administration (both measured in the supine position) for all subjects at baseline and bronchoconstricted conditions.

Region-of-interest analysis. As previously reported (22), methacholine-induced bronchoconstriction generated large and contiguous regions of tracer retention in all subjects (Figure E2). Emission scans acquired by the end of the 3-min washout were thresholded to define a tracer-retaining (TR) region of interest (ROI) for each subject. A nonretaining (NR) ROI of size similar to the TR was identified, and, in most cases, at the same vertical height (Figure 2). The volume of lung encompassed by TR and NR ROIs ranged from 23 to 550 cm^3 and from 34 to 490 cm^3 , respectively (Figure E3). Details of the algorithm used for defining ROIs are in the online supplement.

These ROIs were used to derive values of regional perfusion per voxel ($\dot{Q}$) relative to the mean $\dot{Q}$ outside the ROIs ($\dot{Q}_{\text{TR/Out}}$ and $\dot{Q}_{\text{NR/Out}}$) in baseline and bronchoconstricted conditions. Similarly, regional gas fraction (F_{gas}) for each ROI relative to the mean values outside the ROIs ($F_{\text{gas,TR/Out}}$ and $F_{\text{gas,NR/Out}}$) was calculated from the corresponding transmission scans (27). To assess the extent to which changes in regional lung inflation could affect the measured values of regional perfusion in the TR ROI, regional relative $\dot{Q}$ was normalized by the regional $(1 - F_{\text{gas}})$, which corresponds to the fraction of nongas components (i.e., tissue plus blood) within the TR ROI ($\dot{Q}_{\text{tis}}$). Plots of $\dot{Q}_{\text{tis,TR/Out}}$ versus $F_{\text{gas,TR/Out}}$ were then generated.

For both baseline and bronchoconstricted conditions, the washout kinetics of the average concentration of ^{13}N within each ROI were fitted to a two-compartment model (double exponential washout) with a fast- and a slow-ventilation compartment. The fraction of regional perfusion (F_0) and specific alveolar ventilation (alveolar ventilation per unit volume [sVA]) of each compartment were derived from the model.

Gas exchange impact of the perfusion redistribution during bronchoconstriction. To estimate the effect on $\text{VA}/\dot{Q}$ of perfusion redistribution, $\text{VA}/\dot{Q}$ distributions were generated using a voxel-by-voxel analysis of the tracer kinetics measured by PET, as previously described (28, 29), and compared with $\text{VA}/\dot{Q}$ distributions derived from measured sVA but assuming that the $\dot{Q}$ distribution was uniform throughout the lung.

Statistical analysis. The paired Student's t test was used to assess significance at a level of $p < 0.05$. Data are expressed as mean $\pm$ SD. Further details of the statistical analysis can be found in the online supplement.

RESULTS

Global Image Analysis

Tracer retention. At baseline, a small fraction of the injected ^{13}N tracer was retained in the imaged lung field at the end of the washout (mean $\text{Ftr} = 0.033 \pm 0.055$), although in some subjects small regions of tracer retention (“ventilation defects”) were visible (Figure 3). During bronchoconstriction, there was a substantial increase in total tracer retention (mean $\text{Ftr} = 0.151 \pm 0.085$, $p < 0.001$). In all subjects, such retention occurred in large and contiguous regions that were adjacent to regions of minimal retention. Ventilation defects occurred mostly bilaterally but with various degrees of right-to-left asymmetry (Figures 3 and E2). Pooled data for all subjects showed a negative correlation between the log of Ftr and FEV_1 normalized by the baseline supine FVC at baseline ($r = -0.61$, $p = 0.05$) and during bronchoconstriction ($r = -0.70$, $p = 0.02$; Figure 4).

Regional perfusion. At baseline, the distribution of regional $\dot{Q}$ was relatively uniform (mean $\text{CV}_0^2 = 0.13 \pm 0.07$), with a moderate but significant vertical gradient favoring the dependent regions (mean vertical gradient, $-5.8 \pm 2.4\%/cm$). Bronchoconstriction was accompanied by a significant increase in the heterogeneity of the distribution of regional $\dot{Q}$ (mean $\text{CV}_0^2 = 0.25 \pm 0.18$, $p = 0.012$ vs. baseline). Visual inspection of the $\dot{Q}$ images of Figure 3 illustrates how, during bronchoconstriction, perfusion was typically redistributed away from areas of high tracer retention into areas with low tracer retention. As a result, large regions of low $\dot{Q}$ spatially corresponded to regions of low ventilation and

Figure 1. Protocol schema.

Figure 2. Examples of tracer-retaining (TR; red) and non-tracer-retaining (NR; yellow) regions of interest (ROIs) for two subjects with the smallest (h023) and largest (h006) ROIs. These are three-dimensional renderings of 14 axial slices from the positron emission tomography camera. The lung mask is shown as transparent gray. The *top image* (h023) is oriented as if the subject were upside-down. Also shown are the tracer kinetics for each region fitted with a two-compartment washout ($\text{Activity} = Ae^{-k_1t} + Be^{-k_2t}$). Note the incomplete washout in the TR ROI compared with the NR ROI.

regions of increased $\dot{Q}$ corresponded to areas of high ventilation. This heterogeneous pattern of perfusion resulted in a reduced vertical gradient ($-1.3 \pm 0.06\%/cm$) during bronchoconstriction.

Regional Analysis

Average $\dot{Q}$ per voxel of TR ROIs normalized by the average perfusion of the rest of the lung ($\dot{Q}_{\text{TR}/\text{Out}} = 1.15 \pm 0.14$) significantly decreased ($p < 0.001$) during bronchoconstriction com-

pared with that at baseline conditions (mean change = $-33 \pm 17\%$; Figure 5).

Average $\dot{Q}$ of NR ROIs normalized by the average perfusion of the rest of the lung ($\dot{Q}_{\text{NR}/\text{Out}} = 1.10 \pm 0.21$) increased in 8 of 11 subjects during bronchoconstriction, but the mean change did not reach significance ($p = 0.06$; *right panel* of Figure 5). Although not different at baseline, during bronchoconstriction, $\dot{Q}_{\text{NR}/\text{Out}}$ became significantly greater than $\dot{Q}_{\text{TR}/\text{Out}}$ ($p < 0.001$).

Figure 3. Positron emission tomography images of perfusion and end-washout (End w/o) before (baseline) and after nebulized methacholine (bronchoconstriction) for Subject h021. Each row contains a selected slice of the lung from apex (*top*) to base (*bottom*) over a 10-cm span of lung. In each slice, the left lung is on the *left* and the right lung is on the *right*. Each panel of images is mean-normalized, with the color scale representing the ^{13}N activity. In the perfusion images, note the vertical gradient in perfusion from ventral to dorsal regions at baseline, but the marked heterogeneity of perfusion during bronchoconstriction. Almost all activity is washed out at baseline, but large areas of tracer retention are seen in the end w/o images during bronchoconstriction, and these areas correspond to areas of low perfusion.

Figure 4. Semi-log plots of fraction of retained tracer activity (Ftr) versus FEV₁ normalized by the baseline supine FVC at baseline (*left*) and during bronchoconstriction (*right*) for each subject. At baseline, Ftr was correlated with FEV₁/FVC_{baseline, supine} ($r = -0.61$, $p = 0.045$) and the correlation improved after bronchoconstriction ($r = -0.70$, $p = 0.02$).

Bronchoconstriction also caused a systematic and significant increase in global and regional lung inflation. Indeed, the volume of lung imaged increased by $20 \pm 16\%$ ($p = 0.002$) and global Fgas increased by $6.6 \pm 4.0\%$ ($p < 0.001$) during bronchoconstriction. Regional Fgas in the TR ROI increased by $13 \pm 7.7\%$ compared with that at baseline ($p < 0.001$).

All subjects had a reduction in perfusion to TR ROIs (values of $[\dot{Q}_{TR/Out}]_{BC/baseline} < 1$ in Figure 6A), and all but one had an increase in fractional gas content (values of $[F_{gasTR/Out}]_{BC/baseline} > 1$ in Figure 6A) during bronchoconstriction and two subjects had reductions in regional $\dot{Q}$ to TR ROIs despite the lack of increase in regional Fgas ($[F_{gasTR/Out}]_{BC/baseline} > 1$ in Figure 6A). Note that, even after adjusting $\dot{Q}$ for differences in tissue content caused by differences in regional lung inflation, all but two subjects still demonstrated a reduction in $\dot{Q}$ to TR ROIs with bronchoconstriction ($[\dot{Q}_{tis,TR/Out}]_{BC/baseline} < 1$ in Figure 6B). There was a negative correlation ($r = -0.61$, $p = 0.046$) in the fractional change in relative $\dot{Q}$ to TR ROIs between baseline and bronchoconstriction ($[\dot{Q}_{TR/Out}]_{BC/baseline}$), and their fractional change in relative Fgas between baseline and bronchoconstriction. The correlation was lower and nonsignificant ($r = -0.41$, $p = 0.211$) when regional

perfusion was adjusted to account for the increase in gas content per voxel of TR ROIs ($[\dot{Q}_{tis,TR/Out}]_{BC/baseline}$; Figure 6B).

Calculating $\dot{V}_A/\dot{Q}$ assuming a uniform distribution of $\dot{Q}$ for all subjects resulted in a mean $33 \pm 16\%$ increase in log SD of $\dot{V}_A/\dot{Q}$ (1.03 ± 0.37 to 1.34 ± 0.42 , $p < 0.001$; Figure 7). Perfusion to the low $\dot{V}_A/\dot{Q}$ mode during bronchoconstriction increased by $86 \pm 47\%$ (0.10 ± 0.08 to 0.17 ± 0.10 , $p < 0.001$).

INTRAREGIONAL ANALYSIS

Average results from intraregional analysis are presented in Table 1. Both at baseline and during bronchoconstriction, the washout from TR and NR ROIs was well described by the two-compartment model with very high R^2 values. At baseline, the analysis showed, in both NR and TR ROIs, a fourfold difference between fast and slow compartments' $s\dot{V}_A$ and the greatest fraction of intraregional perfusion (F_0) was associated with the fast compartment. There was, however, no difference in intraregional $s\dot{V}_A$ between the NR and TR ROIs for either the fast or slow compartment at baseline.

During bronchoconstriction in the TR ROI, there was a fourfold reduction of the slow compartment's $s\dot{V}_A$ ($p < 0.001$) and

Figure 5. Ratio of average perfusion inside to outside the TR ROI (*left*) and NR ROI (*right*) at baseline and during bronchoconstriction (BC) for each subject. Solid circles are the individual subjects, whereas the solid bar is the mean. Note the systematic decrease in perfusion to the TR ROI, which was significantly decreased ($p < 0.001$), and the variable change in perfusion to the NR ROI during BC ($p = \text{not significant [n.s.]}$).

Figure 6. (A) The ratio of perfusion ($\dot{Q}$) during BC to baseline versus gas fraction (F_{gas}) during BC to baseline. The perfusion and F_{gas} are expressed as the ratio of mean perfusion or F_{gas} inside the TR ROI to the rest of the lung ($\dot{Q}_{\text{TR/Out}}$ and $F_{\text{gas}_{\text{TR/Out}}}$). Note that almost all points lie in a quadrant bounded by a ratio > 1 for $(F_{\text{gas}_{\text{TR/Out}}})_{\text{BC/baseline}}$ and < 1 for $(\dot{Q}_{\text{TR/Out}})_{\text{BC/baseline}}$ (dashed lines). This indicates that F_{gas} increased and perfusion decreased in TR regions during BC. (B) The same data except that $\dot{Q}$ is now normalized for the tissue content per voxel ($\dot{Q}_{\text{tis}}$). Note that most points still lie in the same quadrant (dashed lines). This means that the reduction in perfusion cannot be simply from lung expansion (decreasing the amount of tissue per voxel). The adjustment of $\dot{Q}$ for the effect of lung expansion reduced the correlation ($r = -0.61$ to $r = -0.41$).

a significant increase in the fraction of intraregional perfusion associated with this compartment ($p < 0.001$), reflecting an increase in the fraction of alveolar units receiving slow ventilation. The fast compartment's $s\dot{V}_A$ of the TR ROIs was not significantly changed by bronchoconstriction but was associated with a reduction in F_O (Figure 8), and thus a reduction in the fraction alveolar units receiving normal ventilation.

As expected, the slow compartment's $s\dot{V}_A$ of NR ROIs was significantly higher than that of TR ROIs ($p < 0.001$). However, there was no difference between the fast compartment's $s\dot{V}_A$ of the two ROIs during bronchoconstriction (Table 1 and top left of Figure 8).

In NR ROIs, the slow compartment's $s\dot{V}_A$ was not significantly changed by bronchoconstriction, but the fast compartment's $s\dot{V}_A$ increased by 21% compared with baseline ($p = 0.04$; Figure 9). During bronchoconstriction, the fast compartment of the NR ROI was associated with most of the intraregional perfusion fraction ($F_O = 0.756 \pm 0.126$) and there was no significant change in the fractional distribution of blood flow between fast or slow compartments in NR ROIs from baseline to bronchoconstriction (Figure 9).

DISCUSSION

In this study, we found a systematic and substantial shift in pulmonary perfusion away from ventilation defects and a concomitant increase in regional expansion in these areas during methacholine-induced bronchoconstriction in patients with asthma. Regional perfusion was reduced by 30% and regional gas content increased by 13% in ventilation defects during bronchoconstriction relative to baseline conditions. To our knowledge, this is the first quantitative assessment in humans of the regional redistribution in pulmonary perfusion with bronchoconstriction. Such redistribution tends to reduce $\dot{V}_A/\dot{Q}$ mismatch by shifting perfusion away from ventilation defects. If such a redistribution had not taken place, the log SD of $\dot{V}_A/\dot{Q}$ would have been 33% greater and perfusion to the lowest $\dot{V}_A/\dot{Q}$ units would have almost doubled.

Before discussing these findings, experimental and methodologic limitations of the study should be acknowledged. General experimental limitations of our PET imaging technique have been discussed in previous reports (27, 29, 30). With our technique, regional $\dot{Q}$ is assessed from the intrapulmonary distribution of the ^{13}NN tracer measured during apnea, whereas regional $s\dot{V}_A$ is assessed from the washout rate of the tracer during breathing. Because the distribution within the lung of ^{13}NN tracer injected intravenously in saline is complete within the first 5 to 10 s of the apnea, it is unlikely that perfusion changed substantially during that short period. Therefore, the tracer distribution

should be a reasonable index of regional perfusion just before the apnea. An inability to maintain mean lung volume during breath-hold may have caused some degree of misregistration between images of ventilation and perfusion. To maximize the likelihood that the same regions of the lung were imaged during both conditions, we instructed subjects to breath-hold at mean lung volume displayed to them superimposed on the real-time signal from the impedance plethysmograph. In addition, to ensure that breathing during the washout period reflected the spontaneous breathing pattern of the subject, and to minimize time variability during breathing, we coached the subjects to follow a breathing pattern previously recorded during a period of normal steady-state breathing that was displayed to them in tandem with the real-time signal.

In this study, bronchoconstriction was induced with methacholine. It is possible that patients with asthma who develop exacerbations could have a different pattern of perfusion redistribution due to the presence of inflammatory mediators or NO production that are not likely present in methacholine-induced bronchoconstriction. Also, these were patients with mild asthma, unlikely to have airway or vascular remodeling that might have altered the redistribution of perfusion with methacholine. Indeed, the heterogeneity in perfusion at baseline in this group was not different from that measured with the same technique in normal individuals (27). Subjects were challenged with methacholine and imaged in the supine position. It is possible that the pattern of ventilation and perfusion in the upright or prone positions could have been different, given the established effects of body posture on ventilation and perfusion (27). It is clear that

Figure 7. Perfusion fraction versus mean-normalized $\dot{V}_A/\dot{Q}$ at baseline (left) and during BC (right) for the same subject shown in Figure 4. In the right panel, the dashed line shows the change in $\dot{V}_A/\dot{Q}$ distribution if all imaged voxels had a perfusion equal to the mean of the lung. Note the greater than 100% increase in perfusion to the lowest $\dot{V}_A/\dot{Q}$.

TABLE 1. TWO-COMPARTMENT WASHOUT ANALYSIS IN TRACER-RETAINING AND NONRETAINING REGIONS

	F_Q		$s\dot{V}_A$		R^2	
	Baseline	BC	Baseline	BC	Baseline	BC
TR						
Slow	0.201 ± 0.170	0.659 ± 0.119*	0.017 ± 0.007	0.004 ± 0.002*	0.997 ± 0.003	0.984 ± 0.021
Fast	0.799 ± 0.170	0.341 ± 0.119*	0.078 ± 0.026	0.069 ± 0.032		
NR						
Slow	0.257 ± 0.216	0.244 ± 0.126	0.019 ± 0.007	0.015 ± 0.006†	0.997 ± 0.002	0.994 ± 0.007
Fast	0.743 ± 0.216	0.756 ± 0.126	0.076 ± 0.028	0.092 ± 0.023*		

Definitions of abbreviations: BC = bronchoconstriction; F_Q = fraction of perfusion to fast and slow compartments; NR = non-tracer-retaining region of interest; $s\dot{V}_A$ = specific alveolar ventilation (s^{-1}); TR = tracer-retaining region of interest.

* $p < 0.05$ compared with baseline.

† $p < 0.05$ compared with TR.

administration of methacholine in the supine position caused a much lower FEV_1 than that measured upright with the same methacholine dose (Figure E4). This effect has been noted by others (31), but it is clear that the methacholine challenge in the supine position caused a greater degree of bronchoconstriction than in the upright position and was not simply the additive effect of methacholine and the reduction in FEV_1 associated with the supine position (32, 33). The change in FEV_1 caused by methacholine relative to the baseline supine position (40%) was greater than the 20% measured for the upright position ($p < 0.001$) and may reflect hyperreactivity caused by a reduction in lung volume (33) of the supine position. Indeed, we found a correlation ($r = 0.63$) between airway hyperresponsiveness and the change in FEV_1 with posture.

Patchiness of Ventilation during Bronchoconstriction

We observed ventilation defects (TR ROIs) of varying size, ranging from subsegmental to lobar. One could theorize that the greater the extent of ventilation defects within the lung, the greater the degree of mechanical obstruction. We found

a negative correlation between the logarithm of total tracer retention fraction and the FEV_1 normalized by the baseline supine FVC (Figure 4). The relationship accounted for about 37 and 49% of the variance in retained tracer at baseline ($r = -0.61$) and during bronchoconstriction ($r = -0.71$), respectively. A similar correlation ($r = -0.71$) was found between FEV_1 and number of defects seen with hyperpolarized helium magnetic resonance imaging (34). This finding suggests that FEV_1 may not be very sensitive to heterogeneity, particularly when it occurs in clusters of severely constricted terminal bronchioles, because the remaining ventilating units of the lung could provide the flow during the initial part of a forced exhalation.

Alterations in Regional Perfusion

Ventilation/perfusion analysis using the multiple-inert gas elimination technique (MIGET) showed a broadening of ventilation/perfusion distributions in asthma (18–21), but no spatial information is provided by that technique. Perfusion defects have been reported in patients with asthma from early scintigraphic measurements of perfusion (11–17). In some of those studies,

Figure 8. Specific ventilation ($s\dot{V}_A$, top row) and fraction of perfusion (F_Q , bottom row) for the fast (left column) and slow (right column) compartments of the TR ROI at baseline and during BC. The decrease in $s\dot{V}_A$ and increase in F_Q in the slow compartment were statistically significant as well as the decrease in F_Q in the fast compartment. Note that F_Q represents the fraction of total perfusion to the ROI and can be thought of as the fraction of alveolar units with either fast or slow $s\dot{V}_A$.

Figure 9. The $s\dot{V}_A$ (top row) and F_Q (bottom row) for the fast (left column) and slow (right column) compartments of the NR ROI at baseline and during BC. Only the increase in $s\dot{V}_A$ after methacholine in the fast compartment was significant. Note that the F_Q represents the fraction of total perfusion to the ROI and can be thought of as the fraction of alveolar units with either fast or slow $s\dot{V}_A$.

perfusion defects were reported to be qualitatively related to ventilation defects after antigen challenge (16) but not after histamine- or exercise-induced (15) bronchoconstriction. Our study demonstrated that, in methacholine-induced bronchoconstriction, regional blood flow was systematically shifted away from regions of increased tracer retention, resulting in perfusion defects that were spatially associated with the ventilation defects. Whether these shifts in perfusion are different in other types of bronchoprovocation is still unclear.

The precise mechanisms responsible for the measured alteration in regional $\dot{Q}$ are also not clear. Because these patients were studied while breathing room air, one likely mechanism could be hypoxic pulmonary vasoconstriction (HPV) of severely hypoventilated alveolar units. Indeed, a large fraction of the intraregional perfusion to TR ROIs (66%) was associated with units in which $s\dot{V}_A$ was, on average, 20 times lower than normal ($s\dot{V}_A = 0.004$ vs. 0.078 in Table 1). Assuming $\dot{V}_A/\dot{Q}$ at baseline was unity and that the regional reduction of 30% in $\dot{Q}$ of the TR ROIs was exclusive to the low-ventilation units of that ROI, $\dot{V}_A/\dot{Q}$ would be about 0.095, a level that would yield an alveolar P_{aO_2} of less than 50 mm Hg, and thus would be sufficiently low to induce HPV (35, 36). (The details of this calculation can be found in the online supplement.) Another possible mechanism for the measured reduction of regional $\dot{Q}$ to ventilation defects could have been an increase in F_{gas} within those regions relative to the rest of the lung as a result of regional dynamic hyperinflation. Lung hyperinflation occurs during bronchoconstriction as a result of increased airway resistance with or without expiratory flow limitation (37–39). In fact, the volume of lung imaged in our subjects increased by $20 \pm 16\%$ ($p = 0.002$) and global F_{gas} increased by $6.6 \pm 4.0\%$ ($p < 0.001$) during bronchoconstriction compared with baseline. Because the depth of the imaging field was constant and the location of the chest was stationary relative to the camera, an increase in the volume of imaged lung, accompanied by an increase in average lung expansion, can only reflect an increase in mean lung volume during bronchoconstriction. More important, the relative regional F_{gas} in ventila-

tion defects ($F_{gas,TR/Out}$) was greater during bronchoconstriction ($[F_{gas,TR/Out}]_{BC/baseline} > 1$ in Figure 6). Increased regional lung expansion could, by simply reducing the number of alveolar units within the imaging voxel, yield a lower regional ^{13}N tracer content compared with that outside the ROI and thus a lower value of measured $\dot{Q}_{TR/Out}$ without any change in vascular resistance. However, a substantial reduction in relative regional $\dot{Q}$ was still present after accounting for such a lung expansion effect (9 of 11 values of $[\dot{Q}_{tis,TR/Out}]_{BC/baseline} < 1$; Figure 6). Thus, we can conclude that the reductions in $\dot{Q}_{TR/Out}$ during bronchoconstriction were accompanied by regional increases in lung expansion but such reductions were not the mere effects of regional reductions in the number of alveolar units per voxel resulting from increased F_{gas} . In other words, regional lung hyperinflation (and thus less measured blood flow per voxel) would be expected to lower measured perfusion by our technique without any change in vascular resistance. However, when we correct the perfusion measurement for this “error,” the perfusion is still reduced to TR regions after bronchoconstriction. Taken together, the results can only be explained by a relative increase in the vascular resistance feeding lung units within ventilation defects, either by mechanical compression of vessels or by active smooth muscle constriction (HPV).

Intraregional Distributions of Perfusion and Ventilation

The fact that the two-compartment model fit the washout data so well (mean $R^2 > 0.99$) is consistent with the bimodal distribution of $\dot{V}_A/\dot{Q}$ documented during bronchoconstriction with PET (29, 30) and with MIGET (18–21). The bimodal behavior is also consistent with a theoretical model (40) predicting bistability of constricted terminal airways and with the helium wash-in behavior in normal subjects after nebulized methacholine (41). More recently, we also demonstrated bimodal and patchy ventilation distributions in bronchoconstricted patients with asthma, which were consistent with a complex interaction between airways and parenchyma in an airway tree (22).

Remarkably, although during bronchoconstriction $s\dot{V}_A$ of the slowly ventilating units of TR ROIs was reduced on average to one-quarter of its baseline value, the fast compartment's $s\dot{V}_A$ was not different from that at baseline. Therefore, ventilation defects cannot be exclusively explained by obstruction of individual conducting airways. Instead, the data are consistent with severely constricted small airways clustered within large regions that also include well-ventilated units.

At baseline, $s\dot{V}_A$ in the TR and NR ROIs was similar for both the fast and slow compartments, suggesting that these ROIs were not intrinsically different before methacholine administration. However, the fast compartment's $s\dot{V}_A$ for the NR ROI was greater during bronchoconstriction than that at baseline and was also higher than the fast compartment's $s\dot{V}_A$ of the TR ROI during bronchoconstriction. This is consistent with the expected redistribution of ventilation away from TR regions. In addition, the F_0 for the slow compartment of the TR ROI was dramatically increased. This means that bronchoconstriction substantially reduced the $s\dot{V}_A$ of a large fraction of the alveolar units within the TR region in greater proportion than the reduction of the regional perfusion to that ROI. The fractional distribution of $\dot{Q}$ between fast and slow compartments did not change with bronchoconstriction for the NR ROI. Taken together, these results demonstrate that, during methacholine-induced bronchoconstriction, ventilation defects are formed by clusters of severely underventilated alveolar units adjacent to normally ventilated units.

In summary, the heterogeneous and patchy regional distribution of ventilation during bronchoconstriction was accompanied by physiologically relevant shifts in perfusion, which tended to reduce the regional mismatch between ventilation and perfusion. Whether these shifts were caused by a passive increase in vascular resistance secondary to local alveolar hyperinflation and/or by active increases in pulmonary vascular tone cannot be determined from this work. The redistribution of blood flow may explain why, even though most patients with asthma (>90%) present to the emergency room with reduced arterial oxygenation during acute exacerbations, only few (14%) have a Pa_{O_2} less than 60 mm Hg (42). Given the highly heterogeneous distribution of ventilation expected in these patients, this is a testament to the ability of the lungs to adapt to wide variations in regional ventilation. Indeed, one could extrapolate that if such ability to redistribute perfusion became impaired, it would cause profound hypoxemia. Long-standing and inadequately treated asthma, with persistent perfusion abnormalities, may also cause remodeling of the pulmonary vasculature in addition to the known remodeling that occurs in the airways (43). However, further studies are required to evaluate the relevance of these mechanisms to clinical asthma.

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